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AND

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INTERNATIONAL RECORD OF MEDICINE

NOBEL PRIZE ADDRESS—STREPTOMYCIN: BACKGROUND, ISOLATION, PROPERTIES, AND UTILIZATION — *Selman A. Waksman*

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NEW DIETARY REGIME IN ULCER THERAPY

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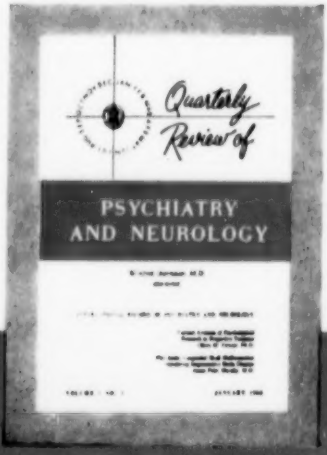

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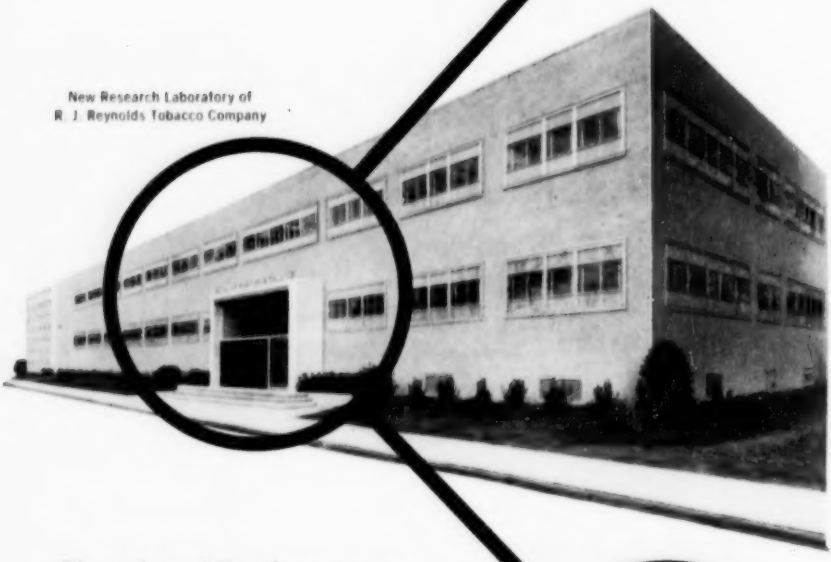

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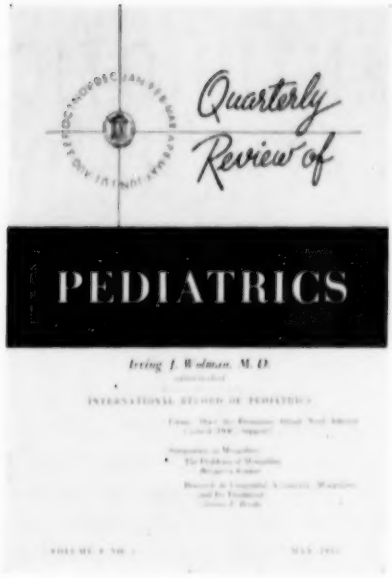

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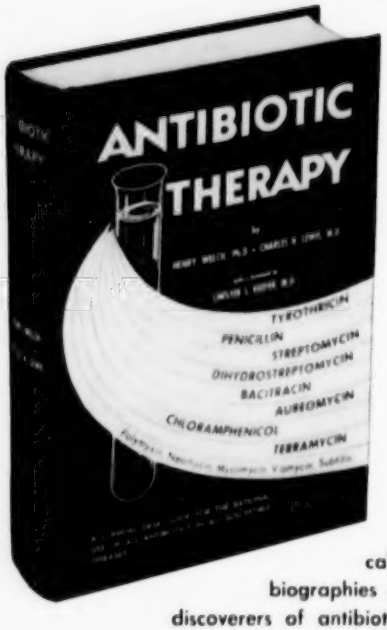

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Nobel Prize Address—Streptomycin: Background, Isolation, Properties, and Utilization 267
Selman A. Waksman

GENERAL PRACTICE CLINICS

Editorial: The Antibiotic-Resistant Staphylococci 281

The Problem of Burns in Disaster 282

Therapeutic Notes

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The Psychologic Implications of Shock Therapy 287
D. W. Abse

PSYCHIATRY ABSTRACTS

Alcoholism and Drug Addiction

The Psychological Mechanism of Alcohol Addiction 294
Some Applications of a Follow-Up Study to Psychiatric Standards for Mobilization 294

Clinical Psychiatry

The Management and Treatment of the Manic-Depressive Syndrome in An Occupational Therapy Clinic 295

Geriatrics

The Aged Mental Hospital Patient 296

Psychiatry and General Medicine

The Psychosomatic Concept in General Medicine 297
The Liaison Psychiatrist: His Role in Gynecology 297
Motility of the Small Intestine During Emotional Reactions 298

Psychiatric Nursing, Social Work and Mental Hygiene

Psychiatry and the Neuropsychiatric Technician 299
Ethical and Psychological Aspects of a Group of Adolescent Misfits 299

NEUROLOGY ABSTRACTS

Clinical Neurology

Tension Headache 300
Neurological Complications Following Antirabies Vaccination 301

Convulsive Disorders

Mesantoin in the Control of Epilepsy 301

BOOK REVIEWS

The Maggid of Caro 302
Books Received for Review 303

NOTES AND ANNOUNCEMENTS 304

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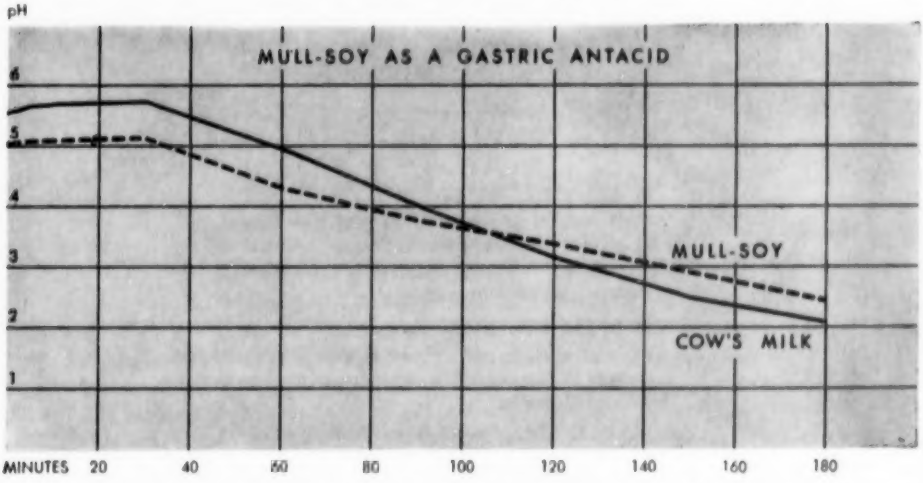

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NOBEL PRIZE ADDRESS

Streptomycin: Background, Isolation, Properties, and Utilization*

Selman A. Waksman

INSTITUTE OF MICROBIOLOGY

RUTGERS UNIVERSITY, NEW BRUNSWICK, N. J.

The highest scientific award and honor presented to me today gives me the opportunity to summarize briefly the discovery and utilization of streptomycin for disease control, notably in the treatment of tuberculosis, the "Great White Plague" of man.

HISTORICAL BACKGROUND

Streptomycin belongs to a group of compounds, known as antibiotics, which are produced by microorganisms and which possess the property of inhibiting the growth and even of destroying other microorganisms. Antibiotics vary greatly in their chemical nature, mode of action upon different organisms, and effect upon the animal body. The selective action of antibiotics upon bacteria and other microorganisms is known as the antibiotic spectrum. Some antibiotics are characterized by a very narrow spectrum, whereas others possess a wide range of activity. Some are active only against certain bacteria and not upon others, whereas some are active against fungi, and some against viruses. There is not only considerable qualitative variation in the activity of different antibiotics, but also wide quantitative differences. Antibiotics are produced by bacteria, fungi, actinomycetes, and to a limited extent by other groups of microorganisms.

It has been known for more than six decades that certain fungi and bacteria are capable of producing chemical substances which have the capacity to inhibit the

*Nobel Prize Address, delivered at the Caroline Institute in Stockholm, Sweden, on December 2, 1952.

growth and even to destroy pathogenic organisms. Only within the last 12 or 13 years, however, have antibiotics begun to find extensive application as chemotherapeutic agents. Among these, penicillin and streptomycin have occupied a prominent place. Penicillin is largely active upon gram-positive bacteria, gram-negative cocci, anaerobic bacteria, spirochetes, and actinomycetes; streptomycin is active against a variety of gram-positive and acid-fast bacteria, as well as upon gram-positive organisms some of which have become resistant to penicillin. Neither of these antibiotics is active upon rickettsiae, viruses, and fungi. They too differ in their physical and chemical properties and in their toxicity to animals.

Since the discovery of streptomycin, the production and clinical application of this antibiotic have had a phenomenal rise. The streptomycin-producing strain of *Streptomyces griseus* was first isolated in September 1943, and the first public announcement of the antibiotic was made in January 1944. Before the end of that year, streptomycin was already being submitted to clinical trial. Within two years, the practical potentialities of streptomycin for disease control were definitely established.

The most spectacular of all the clinical applications followed recognition that streptomycin was highly effective against the tuberculosis organism, not only *in vitro* but also *in vivo*. Several clinical centers undertook to test the sensitivity of different freshly isolated strains of *Mycobacterium tuberculosis* to streptomycin, its practical evaluation in control of tuberculosis in experimental animals, and finally its use in the control of tuberculosis in the human body. Following the lead of Dr. William H. Feldman and Dr. H. Corwin Hinshaw at the Mayo Clinic, the American Trudeau Society and the National Tuberculosis Association took an active part in these investigations. The first conference arranged for the evaluation of the clinical results of the use of streptomycin was held in 1945, and others soon followed.

Within three years after the announcement of the isolation of streptomycin came the almost complete elucidation of its chemistry, its first derivative (dihydrostreptomycin) was obtained, and the first 1,000 clinical cases were reported. From a laboratory curiosity, streptomycin production soon grew into a large industry, with a monthly output of more than 25 thousand kilograms in the United States alone, and with many plants being established abroad for its manufacture.

This marked rise in the development of streptomycin was due partly to the fact that the spectacular increase, between 1941 and 1943, in the use of penicillin for disease control suggested the possibility that there were other antibiotics which could be utilized for the treatment of diseases not sensitive to penicillin. It was the knowledge of the great abundance and wide distribution of actinomycetes, which dated back nearly three decades, and the recognition of the marked activity of this group of organisms against other organisms that led me in 1939 to undertake a systematic study of their ability to produce antibiotics. Between 1940 and 1952 we isolated in our laboratories 10 different chemical substances from cultures of different actinomycetes, beginning with actinomycin and ending with candicidin. Of these, streptomycin proved to be by far the most important chemotherapeutic agent.

The isolation of streptomycin was the culminating point of a painstaking search for antimicrobial agents produced by actinomycetes, a group of organisms closely related to the bacteria. This was preceded by long and continuous research, dating back to 1915, on actinomycetes, their occurrence and abundance in nature, their systematic or taxonomic position, their rôle in soil processes, notably in the decomposition of plant and animal residues and in the formation of humus, and finally their associative and antagonistic effects upon bacteria and fungi. It was finally established that as many as 20 to 50 per cent of all the actinomycetes found in the soil and in other natural substrates had the capacity to inhibit the growth of other microorganisms.

Streptomyces griseus, the organism which comprised the streptomycin-producing strain, was known in our laboratories from the beginning of our work on actinomycetes, although it was not tested at that time for its antibiotic-producing properties. The ability of actinomycetes to exert injurious effects upon bacteria and fungi has been known for many years. Lieske showed in 1921 that certain strains are able to bring about lysis of many bacteria and antagonize their growth. This process is selective in nature: some of the bacteria are affected, and others are not. Other investigators, notably Gratia and Dath and Rosenthal, demonstrated in 1925 that cultures of organisms designated as *Streptothrix*, and now known to be actinomycetes, are capable of dissolving living and dead bacterial cells. Nakhimovskaia in 1937 made the first survey of the occurrence of antagonistic actinomycetes in the soil: 80 cultures were isolated, of which 47 were able to repress bacterial growth, but only 27 liberated into the medium substances which had the capacity to inhibit the growth of gram-positive bacteria, but not of gram-negative bacteria or fungi.

When we began our investigation on the production of antibiotics by actinomycetes in 1939, only two preparations were known to possess antimicrobial properties. These were not true antibiotics, or at least were not recognized as such. One was obtained by Gratia and had the capacity to lyse dead typhoid cells and certain living bacteria; it was later designated by Welsch as actinomycetin. The other was believed to be a lysozyme, which had lytic principles, and was studied by Krassilnikov and Koreniako in 1939.

The first true antibiotic to be derived from a culture of an *Actinomyces* was isolated in our department in 1940. The organism, *Actinomyces antibioticus*, yielded a substance which was designated as actinomycin. It was soon crystallized, and its chemical and biological properties were established. This antibiotic proved to be a quinone-like pigment with an approximate molecular formula of $C_{11}H_{56}N_8O_{11}$. It was highly active against various gram-positive bacteria but to a much lesser degree against the gram-negative organisms. It proved to be extremely toxic to experimental animals.

This practical failure was followed by a comprehensive program of screening actinomycetes for their ability to produce different antibiotics. The fact was revealed that these antibiotics vary greatly in their chemical nature, toxicity to animals, and antimicrobial activities. Some were active against bacteria and actinomycetes, but not upon fungi; some were largely active against certain bacteria, especially the gram-positive types, but not, or to only a limited extent, against the gram-negative forms,

whereas others were active alike against various gram-positive and gram-negative bacteria. Some had a very narrow spectrum, being active only or largely upon one group of organisms, such as the mycobacteria, or only upon certain fungi, such as yeastlike forms, or upon certain viruses, such as the influenza B types; others had a much wider spectrum, being active upon both bacteria and fungi, or upon bacteria, rickettsiae, and the larger viruses.

It was further found in our laboratory and in others that one antibiotic, such as actinomycin and streptothricin, could be produced by several different species. Some organisms give rise to different modifications of the same antibiotic, as actinomycin A, B, and C. This is true also of streptomycin, various modifications of which are produced by different species of *Streptomyces*, notably *S. griseus*, *S. bikiniensis*, and *S. griseocarneus* (streptomycin, mannosidostreptomycin, hydroxystreptomycin). Some organisms produce a mixture of different antibiotics, as in the case of different strains of *S. griseus*, which give rise not only to streptomycin, but also to the antifungal agents actidione and candicidin.

ISOLATION OF STREPTOTHRICIN AND STREPTOMYCIN

The isolation of actinomycin, the first true antibiotic from a culture of an *Actinomyces*, pointed a way to the formation and isolation from species belonging to this group of organisms of other chemical substances possessing antimicrobial properties. A new type of substance, designated as *streptothricin*, was soon isolated, in 1942. It showed distinct promise as a chemotherapeutic agent. It was active against both gram-positive and gram-negative bacteria and did not appear to be very toxic for animals. The organism producing it was identical with *Actinomyces lavendulae*, a culture found in the soil 25 years previously. This new substance possessed highly desirable physical, chemical, and antimicrobial properties and gave promise of filling the gap left by penicillin in the treatment of infectious diseases due to gram-negative bacteria. It was a basic compound soluble in water, with an optimum activity at slight alkalinity. It was active against a number of bacteria, not only *in vitro*, but also *in vivo*, as well as against various fungi. It was resistant to heat and to the action of different microorganisms and enzymes. A study of its pharmacology, however, brought out the fact that streptothricin exerted a residual toxic effect upon the animal body; its use in the treatment of infectious diseases was, therefore, limited.

The experience gained in the study of streptothricin made possible effective planning of a more comprehensive study of the production of a definite type of antibiotic by actinomycetes. Particular attention was paid to substances that possessed chemical and biological properties similar to those of streptothricin but that would be less toxic to the animal body. The method of cultivation of the organism, notably the use of submerged cultures; the method of isolation of the active substance, notably its adsorption on charcoal and its removal with dilute acid; the method of evaluation of its microbial properties, notably its activity against gram-negative bacteria, were now well understood. It was, of course, desirable that any new substance should possess a spectrum which would be broader than that of streptothricin, that it be particularly active against a greater variety of bacteria which were resistant to peni-

cillin, and, if possible, that it be active against tuberculosis. (Streptothricin was later found also to possess this property.) Less than six months after many freshly isolated cultures of actinomycetes were screened, an organism was obtained which appeared to produce the long-looked-for antibiotic.

Since actinomycin was named after the organism that gave the name to the group of actinomycetales (*Actinomyces* by Harz in 1877), since the first promising antibiotic, streptothricin, was derived from the first name given to a member of this group (*Streptothrix* by F. Cohn in 1872), it was logical that the first chemotherapeutically active substance should be designated by the newly coined generic name of actinomycetes (*Streptomyces* by Waksman and Henrici in 1943). Thus streptomycin was born.

The organism producing streptomycin was identical with a culture isolated in our laboratory in 1916 and described at that time as *Actinomyces griseus* (changed, according to the 1943 classification, to *Streptomyces griseus*). Although numerous additional cultures of streptomycin-producing strains of *S. griseus* have since been isolated, it is one of the 1943 cultures that has been utilized for the commercial production of streptomycin all over the world.

In addition to streptomycin, *S. griseus* was later found to produce mannosidostreptomycin, as well as certain other antibiotics, such as actidione and streptocin. Other strains of this organism produce no antibiotics at all or are able to form other substances, such as grisein and candicidin.

The medium used for the production of streptomycin contained organic sources of nitrogen and carbon, mineral salts, and certain growth-promoting substances. The culture had to be well aerated and incubated at 25 to 30° C. for three to five days. The activity of streptomycin reached 100 to 200 mcg./ml.; in commercial production, much higher yields are usually obtained.

Recovery of the streptomycin was accomplished in a series of operations involving removal of the mycelium by filtration, adsorption of the streptomycin on activated carbon or on some other absorbent, elution by dilute acid, neutralization of the eluate, concentration by evaporation and dehydration or by solvent precipitation, and filtration and drying. Various methods have been used for further purification and crystallization of the antibiotic.

Streptomycin was found to be soluble in water and insoluble in organic solvents, such as ether, chloroform, and acetone. The chloride was completely soluble in methanol, less soluble in ethanol, and virtually insoluble in butyl alcohol, acetic acid, and pyridine. The sulfate was only slightly soluble in methanol and virtually insoluble in the other solvents.

A unit of streptomycin was designated as that amount of material which was just sufficient to inhibit the growth of a standard strain of *Escherichia coli* in 1 milliliter of culture medium. When streptomycin was later isolated in a crystalline state, it was found that 1 unit was comparable to 1 microgram of the pure base. The United States Food and Drug Administration, in consultation with the different manufacturers, decided to establish the potency of streptomycin on the basis of the weight of the active material.

The activity of streptomycin against sensitive organisms was found to be influenced by the presence of certain chemical compounds. Glucose reduced its activity

appreciably; hydroxylamine, thioglycollate, and cysteine largely inactivated it. This phenomenon was utilized in testing for sterility of streptomycin preparations or for determining the admixture of other antibiotics. The activity of streptomycin was found to be influenced but little by body fluids, pus, or normal tissue juices. The optimum reaction was 8.0; increasing acidity resulted in a decreased bacteriostatic potency, the greatest reduction taking place between *p*H 6.6. and *p*H 5.9.

CHEMICAL NATURE OF STREPTOMYCIN

Streptomycin belongs to the glucosides in which a diguanido-group is linked to a nitrogen-containing disaccharide-like compound. It is a strong base, with three basic functional groups. The molecular weight determination on the trihydrochloride in water gave about 800 for the free base after the necessary corrections for the chloride ion.

Upon hydrolysis, it splits into two compounds:

$$\underset{\text{Streptomycin}}{C_{21}H_{39}N_7O_{12}} + H_2O \rightarrow \underset{\text{Streptidine}}{C_8H_{18}N_6O_4} + \underset{\text{Streptobiosamine}}{C_{13}H_{23}NO_9}$$

On further hydrolysis with strong mineral acids, the streptobiosamine gives a 6-carbon sugar and glucosamine:

$$\underset{\text{Streptobiosamine}}{C_{13}H_{23}NO_9} + H_2O \rightarrow \underset{\text{Streptose}}{C_6H_{10}O_5} + \underset{\text{N-methyl-l-glucosamine}}{C_7H_{15}NO_5}$$

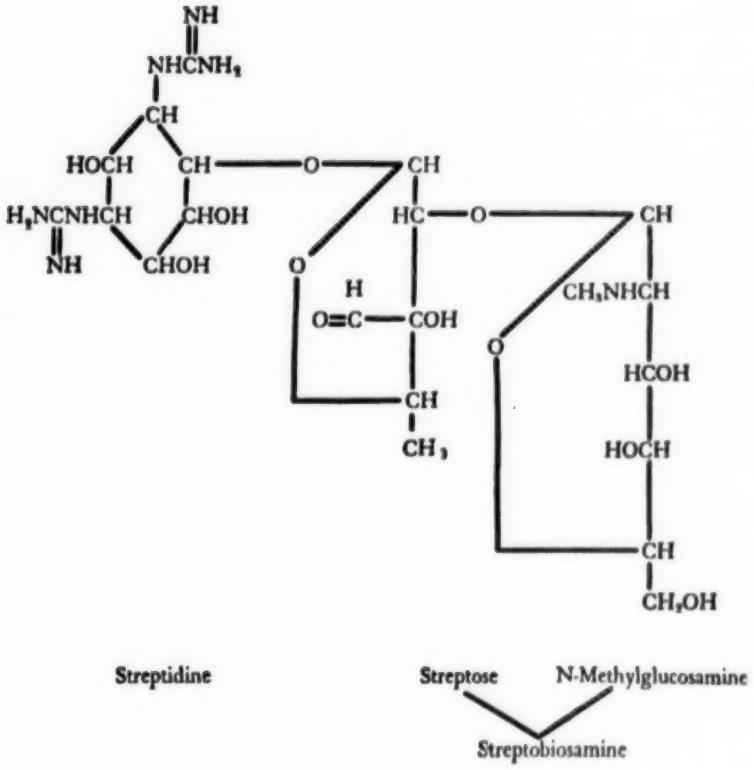
The basic nitrogen atom in the streptobiosamine is not present as a primary amino group.

The structure of the streptomycin molecule is given on page 273.

ANTIBACTERIAL PROPERTIES OF STREPTOMYCIN

Streptomycin is active against a large number of bacteria found among the gram-negative, gram-positive, and acid-fast groups and among the spirochetes; it has relatively little activity against anaerobic bacteria, fungi, protozoa, and viruses. No absolute value can be given for the sensitivity of an organism to streptomycin; this depends not only upon the particular species, but also upon the strain of the organism and upon the composition of the medium in which it is tested. Thus any given figure for a single organism is quite arbitrary, since such values can vary greatly.

Streptomycin is more active upon bacteria in young, actively growing cultures than in older cultures, although this difference does not appear to be so great as that for penicillin. When added to a 3-hour-old culture of *E. coli*, 2 mcg. streptomycin reduced the numbers by 75 per cent, and 5 mcg. by 95 per cent; the corresponding reductions for 24- to 48-hour-old cultures were 19 and 42 per cent. The size of the inoculum influences the bacteriostatic concentration of streptomycin: for instance, an inoculum of 30,000 cells of *Brucella abortus* required 1 mcg./ml. for inhibition of



growth, whereas an inoculum of 30,000,000 cells required 4 mcg./ml. Less streptomycin was needed to inhibit growth of various strains of *Br. abortus* and *Brucella suis* under aerobic conditions than in the presence of 10 per cent CO_2.

Since streptomycin is not active against viruses, it can be utilized in their isolation and purification from bacterial infections. It also is used in the preservation of bull semen, in the purification of cultures of *Trichomonas vaginalis* and *Trichomonas foetus*, and in the development of media for the isolation of pathogenic fungi. Because of its marked antibacterial properties, streptomycin can be used in preventing wound infections and in surgical operations.

Among the antimicrobial properties of streptomycin, its bacteriostatic and bactericidal action upon different strains of *Mycobacterium tuberculosis* is particularly significant. In concentration of 0.05 mcg./ml., it has been found capable of inhibiting growth of the human pathogen to a limited extent, 0.2 mcg./ml. inhibits growth to a marked extent, and 0.4 mcg./ml. stops growth completely, after an incubation time of 16 to 20 days. In other experiments, streptomycin gave complete inhibition of growth of *M. tuberculosis* in concentrations of 0.3 mcg./ml., although occasional

colonies occurred even with 0.5 mcg./ml. The bactericidal action of streptomycin also varies with its concentration and the length of contact with the organism, 0.3 mcg./ml. exerting a marked effect in 48 hours, and 20 mcg./ml. in 6 hours.

RESISTANCE OF BACTERIA TO STREPTOMYCIN

The problem of variation in sensitivity of different strains of the same organism to streptomycin and the increasing resistance of the bacteria on prolonged contact with it are of considerable theoretical and practical importance. Variation in sensitivity may differ from day to day. This is believed to be due, at least in part, to variations in the number of viable organisms, age, and density of the culture, and the particular species involved.

Freshly isolated cultures of tubercle bacilli from patients with pulmonary tuberculosis are uniformly sensitive to streptomycin. When the cultures are exposed to relatively low concentrations of this antibiotic, growth of multiplying cells but not that of the nonmultiplying cells is inhibited. The organism develops resistance to streptomycin *in vitro* at a rapid rate, and this resistance persists for a considerable time; it is not accompanied by any diminution in virulence. In a growing culture of tubercle bacilli, there was found to be, however, a decrease in the proportion of streptomycin-resistant cells with an increase in the age of the culture. The principal effects of streptomycin on the morphology of the organism were a loss of acid-fastness, an increase in granulation, and, in highly bacteriostatic concentrations, a shortening of the rods.

Successive transfers of bacteria commonly occurring in infections of the urinary tract resulted in an increase in resistance to more than 1,000 mcg./ml. of streptomycin. After 29 subsequent daily transfers on common media, the bacteria lost none of their resistance. It was suggested, therefore, that streptomycin-fastness may be a major factor in the failure of streptomycin therapy in certain infections. When the disease condition presents physical barriers to the penetration of the streptomycin, as in cases of abscesses and pyelonephritis, the organisms are exposed to sublethal concentrations, thus resulting in increased resistance. In infections with *Aerobacter cloacae*, an increase of more than 1000 times was obtained after 36 days of treatment.

STREPTOMYCIN IN EXPERIMENTAL INFECTIONS

Streptomycin proved to be highly effective in the treatment of a large number of infectious diseases brought about in experimental animals by various bacteria. This was true of *Salmonella schottmulleri*, *Shigella gallinarum*, *Brucella abortus*, *Pseudomonas aeruginosa*, *Klebsiella* or *Friedländer's bacillus*, *Diplococcus pneumoniae*, and a number of organisms commonly found in urinary tract infections.

Subcutaneous doses of 100 to 200 mcg. of streptomycin were sufficient to protect mice against lethal infections with *S. schottmulleri*. Oral doses of about 3 mg. were required to protect mice infected by the intraperitoneal injection of 10 lethal doses. Following oral administration, streptomycin remained in the intestinal tract and gave very low blood concentrations. Urine recoveries in the animals ranged from

70 to 80 per cent when streptomycin was given parenterally and less than 10 per cent when given orally.

The effectiveness of streptomycin against tularemia, caused by *Pasteurella tularensis* has been most striking. Complete protection was also obtained in experimental infections due to *Proteus vulgaris*: in chick embryos, 1,000 mcg. of streptomycin were required to arrest 18 hour infections; to protect 50 per cent of the embryos, 250 mcg. in a single dose or 150 mcg. in three daily doses were required. Excellent protection was obtained by the use of 150 mcg. streptomycin against fowl typhoid caused by *Sh. gallinarum* in 11 day old chick embryos.

Streptomycin was also found to have a marked effect upon experimental plague, *Pasteurella pestis* being inhibited by 1 mcg./ml. A series of mice infected with the organism were treated with 400 mcg. streptomycin daily, beginning two days after inoculation and continuing for six days. Nine of the ten mice survived 14 days, as compared with the survival of four out of eleven for sulfadiazine-treated mice and one out of nine for the controls. Experimental infections caused by *D. pneumoniae* and *Staphylococcus aureus* were readily controlled when adequate doses of streptomycin were employed.

Of particular importance was pioneering work done by Feldman and Hinshaw[17] on the effectiveness of streptomycin in experimental tuberculosis in guinea pigs. On the basis of an arbitrarily established index of infection, microscopically determined, 100 represented the maximum possible amount of tuberculosis. The control animals, sacrificed after 61 days, exhibited an index of 67 as contrasted to 5.8 for those which had received streptomycin. In another experiment, the corresponding values were 81.9 for the untreated and 2.8 for the treated animals. The daily administration of streptomycin per guinea pig varied from 1,387 to 6,000 mcg. Two different strains of the human tubercle bacillus were equally sensitive to streptomycin. *M. tuberculosis* was recovered from the spleens of only one of the guinea pigs treated with streptomycin, the animal having received 1,387 mcg. streptomycin daily for 54 days.

The conclusion was reached that streptomycin is the most effective tuberculochemotherapeutic agent so far studied. Its relatively low toxicity for guinea pigs, its high efficacy in resolving and suppressing what would otherwise be lethal tuberculosis, established streptomycin as a drug worthy of serious consideration for the treatment of tuberculosis.

TOXICITY OF STREPTOMYCIN

To produce toxic manifestations of streptomycin in animals, it was necessary to administer either extraordinarily large doses of the pure material or smaller amounts of certain impure preparations. No correlation was obtained between the acute toxicity of different lots to experimental animals and clinical tolerance by human beings. The behavior of the material in man could not, therefore, be foretold if antibacterial potency alone was assumed to be the criterion of purity; highly concentrated material had on occasion been unsatisfactory clinically, whereas less active preparations had often produced no undesirable effects.

Among the various toxic reactions resulting from the administration of streptomycin, the otic complications received particular attention. In one experiment, 81 patients treated with streptomycin were examined for evidence of aural toxicity. Two months after cessation of therapy, 3 of these patients showed an absence of vestibular response. During the third month after therapy, one of these three showed increasing recovery of response. All three complained spontaneously of dizziness, which decreased steadily during treatment. One patient showed a high tone loss, but the audiogram was normal in these 3 patients. Another patient showed a severe loss of hearing two weeks after treatment; two weeks later he had shown decided improvement in hearing; he had a normal vestibular response throughout. It was not certain that the low tone and high tone losses were due to streptomycin.

DISEASES RESPONDING TO STREPTOMYCIN

A variety of human and animal diseases caused by various bacteria respond readily to streptomycin treatment. This was brought out in the first comprehensive study of a group of diseases which could be considered to be definitely controlled by streptomycin or to give promise that they would respond favorably. These included tularemia, urinary tract infections, especially those resistant to sulfa drugs and to penicillin, *Klebsiella* and *Hemophilus* infections, bacteremia due to penicillin-resistant organisms, various forms of meningitis, and whooping cough. Streptomycin was also found to be helpful in treatment of a variety of other diseases, such as leprosy, brucellosis, certain forms of tuberculosis, and probably also bacillary dysentery, cholera, and bubonic plague.

The Committee on Chemotherapy, originally organized by the Committee on Medical Research of the OSRD, undertook the supervision and coordination of the first large-scale series of investigations on the use of streptomycin in the treatment of bacterial infections. The various infectious diseases were divided, in their relation to streptomycin, as follows:

Diseases definitely indicated for streptomycin treatment:

1. All cases of tularemia
2. All cases of *H. influenzae* infections:
   - Meningitis
   - Endocarditis
   - Laryngotracheitis
   - Urinary tract infections
   - Pulmonary infections
3. All cases of meningitis due to:
   - *E. coli*
   - *Pr. vulgaris*
   - *K. pneumoniae*
   - *B. lactis-aerogenes*
   - *Ps. aeruginosa*
   - *S. paratyphi*

4. All cases of bacteremia due to gram-negative organisms
   - *E. coli*
   - *Pr. vulgaris*
   - *A. aerogenes*
   - *Ps. aeruginosa*
   - *K. pneumoniae*
5. Urinary tract infections due to
   - *E. coli*
   - *Pr. vulgaris*
   - *B. lactis-aerogenes*
   - *H. influenzae*
   - *Ps. aeruginosa*

Streptomycin found to be a helpful agent but position not yet definitely defined:

1. Peritonitis due to gram-negative bacilli.
2. *B. Friedlander's* pneumonia.
3. Liver abscesses due to gram-negative bacilli.
4. Cholangitis due to gram-negative bacilli.
5. Penicillin-resistant but streptomycin-sensitive organisms infecting heart valves.
6. Tuberculosis.
7. Chronic pulmonary infections due to mixed gram-negative flora.
8. Empyema due to gram-negative infections.

The Committee evaluated the first 1,000 cases treated with streptomycin. In 409 urinary tract infections, the general recovery rate was 42 per cent. Of 100 *H. influenzae* meningitis infections, recovery was obtained in 79 per cent; in 17 of the fatal cases, treatment was too late to be effective. In 14 cases of meningitis caused by other gram-negative organisms, only 4 died. In 91 bacteremia cases, 49 recovered, 12 improved, 4 showed no response, and 26 died; in this group as well, the fatal cases were treated too late. Striking results were obtained in tularemia (63 recoveries out of 67 cases), and in otitis media (7 immediate recoveries out of 8 cases). In 44 cases of pulmonary infections, recovery or improvement was obtained in 61 per cent. Streptomycin was extremely effective against acute *Friedlander bacillus* infections.

In the evaluation of streptomycin in tuberculosis, 75 cases were used. These included miliary, meningeal, larynx, skin, and renal tract forms. It was recommended that a minimum period of treatment should be three to six months with daily doses of 1.5 to 3.0 Gm. Hinshaw, Feldman, and Pfuetze, on the basis of treatment of 100 tuberculosis cases, came to rather optimistic conclusions that streptomycin was an antibacterial agent which possesses the unique ability to inhibit the growth of *M. tuberculosis* both experimentally and clinically. It was recommended

that treatment of tuberculosis consist of large doses of streptomycin for prolonged periods.

Various forms of tuberculosis were soon found to respond promptly to streptomycin. These included ulcerating tuberculous lesions of the larynx, hypopharynx, and the tracheobronchial tree, which received combined intramuscular and aerosol treatment. Some types of extrapulmonary tuberculosis also responded well, especially chronic, long-standing draining sinus tracts, which usually closed within a few weeks. These remained closed only if treatment was continued for several weeks after superficial healing. Encouraging results were also obtained in treatment of tuberculosis of bones and joints. Some patients with early tuberculous meningitis responded promptly to adequate intramuscular and intrathecal administration, but frequently these gains were not permanently sustained; temporary clinical remission was frequently realized after streptomycin treatment of early but acute and severe tuberculous meningitis; consciousness could be regained, sometimes within a few days, fever would decline within a few weeks, the patient appearing normal for several months; subsequent exacerbations of the disease were likely to occur and were not likely to respond to treatment.

Disseminated hematogenous tuberculosis of the miliary type heretofore did not respond to treatment, spontaneous recoveries being extremely rare. By the use of streptomycin it was possible to bring about a complete clinical and roentgenologic remission. Tuberculosis of the alimentary tract and tuberculous peritonitis also showed striking symptomatic improvement.

The rapid progress made in the use of streptomycin in tuberculosis was thus well expressed by Walker, Hinshaw, and Barnwall: "The introduction of streptomycin into clinical medicine has been peculiarly exciting to phthisiologists. Not only have they never had an 'antibiotic' which was helpful in the treatment of tuberculosis in man, they have never had a proved effective drug of any sort. So far as chemotherapy is concerned not only was their situation comparable to that of the syphilologist prior to the discovery of penicillin, it was worse than his position before the appearance of Ehrlich and arsenic. Phthisiologists have been dependent on rest in bed, and, more recently, on collapse therapy. The relatively rapid evaluation of a new drug—rapid for tuberculosis if not for pneumococcic pneumonia—is partly the result of experience gained from the investigation of other drugs in other diseases. It is partly a result of the employment, here and in England, of cooperative methods of investigation which have yielded data, reasonably uniform, rapidly, and in large amount."

I need hardly survey the subsequent developments in the use of streptomycin for the different infectious diseases, especially tuberculosis. I need hardly dwell upon the various regimens for treatment, based on special dosages and modes of administration, and its combined use with para-amino-salicylic acid (PAS). I need not list the numerous antibiotics that have been isolated from cultures of actinomycetes, some in our own laboratories, such as neomycin, and some in numerous other laboratories throughout the world. Suffice to say that streptomycin pointed the way, both through the planned screening programs and through its specific activity against the

gram-negative bacteria and tuberculosis, to many of these antibiotics. The rest is history. Medical science and clinical practice have been revolutionized. One may look forward to further discoveries of agents that will combat diseases not now subject to therapy, to more active and less toxic agents than those now available, and to combined therapy of several antibiotics or of antibiotics and synthetic compounds which will prove to be more effective than the use of single substances.

SUMMARY

The discovery of streptomycin as a product of a rather obscure group of microorganisms, the actinomycetes, led to the study of these organisms as potential producers of other chemotherapeutic substances. Following streptomycin, there came in rapid succession chloramphenicol, aureomycin, neomycin, terramycin, and, more recently erythromycin and others. These antibiotics have found extensive application as chemotherapeutic agents in the treatment of numerous infectious diseases never before subjected to therapy.

In the treatment of tuberculosis, the more controlled dosage of streptomycin and the supplementary use of PAS tended to overcome some of the limitations of the antibiotic, notably its toxicity and the development of bacterial resistance. The recent introduction of isonicotinic acid hydrazide suggests the possibility that its combined use with streptomycin will tend further to control the disease and overcome undesirable complications. The conquest of the "Great White Plague," undreamt of less than 10 years ago, is now virtually within sight.

ACKNOWLEDGMENTS

I wish to take this opportunity to thank all my collaborators, associates, and graduate students who have participated in the investigations necessary to the development of our broad antibiotic program. Special thanks are due to the following assistants and graduate students: Misses Elizabeth S. Horning, Elizabeth Bugie, Doris Jones, D. Hutchinson, H. C. Reilly and Dorothy G. Smith; Drs. M. Welsch, W. Geiger, W. Garson and E. A. Swart; and Messrs. H. B. Woodruff, Albert Schatz, H. Lechevalier, S. R. Green, D. A. Harris, W. P. Iverson, D. Reynolds, H. J. Robinson, and Otto Graessle; to the chemists, pharmacologists, bacteriologists, and engineers of Merck & Company; to Drs. W. H. Feldman and H. C. Hinshaw of the Mayo Clinic; to Dr. C. S. Keefer of the Committee on Medical Research; and to numerous clinical investigators who have helped to make streptomycin the important chemotherapeutic agent it is today.

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GENERAL PRACTICE CLINICS

17. *Editorial: The Antibiotic-Resistant Staphylococci.* HENRY WELCH, Washington, D. C. Antibiotics and Chemotherapy, 3:561–70, June 1953.

Over a period of several years there have been numerous reports emphasizing the increase in frequency with which staphylococci (micrococci) resistant to one or more of the antibiotics are encountered. It is imperative that these developments be seen in their true perspective so that no patient who really needs penicillin or a broad spectrum antibiotic, and their number is legion, be denied the benefits of such medication whenever clinically indicated. This editorial reveals the problem of antibiotic-resistant staphylococci as it relates to such valued agents as penicillin and the broad spectrum antibiotics. The apparent increase in antibiotic-resistant staphylococci is being magnified by the results observed in studies of *hospital* communities. It appears from a careful review of the literature that the incidence of antibiotic-resistant staphylococci has increased to a considerably less degree than has been indicated by studies made of staphylococci strains isolated from hospital patients. Micrococci naturally resistant to penicillin were isolated prior to the use of penicillin in the treatment of human infections and it is probable that some 10–11 per cent of these organisms were initially resistant to this drug. The reports that have been accumulated concerning the increase in resistant staphylococci have been invariably the results of studies on hospitalized patients. Incidences of resistant staphylococci reported in these studies have varied from 40 to 80 per cent. Similar studies either on outpatients or the community at large have resulted in the isolation of resistant staphylococci in percentages not markedly different from those reported prior to the clinical use of penicillin. From studies made in England, Australia, Norway, France and the United States, it is apparent that the high incidence of infection due to resistant staphylococci is the result of hospital cross-infection.

Some of the resistant staphylococci have caused "micrococcic enteritis," an extremely serious and oftentimes fatal infection, following the use of various antibiotics. Several cases may occur in a hospital population, all the result of cross-infection either from fomites, from patient-to-patient or from carriers among the hospital personnel. Certain of the other antibiotics may be of value in the treatment of this disease: erythromycin, carbomycin, chloramphenicol, or bacitracin.

The status of the problem at this time appears to be as follows: (a) There has been an increase in the numbers of penicillin-resistant staphylococci. To a lesser degree, the same may be said of the other available antibiotics; (b) The increase in antibiotic-resistant staphylococci has been magnified and overemphasized by the results observed in studies of hospital infections. Since these are largely caused by cross-infections, the high incidence of resistant organisms found does not reflect the actual situation. In all instances the incidence of antibiotic resistant organisms is greater in hospitalized than in nonhospitalized populations. (c) Cross-infections occur not only from patient-to-patient, but also from carriers among the hospital

personnel as well; (d) There are drugs available that may be quite successful in the treatment of resistant staphylococcal infections: erythromycin, carbomycin, bacitracin, and chloramphenicol. Even now, however, resistant strains are beginning to emerge with such new antibiotics as erythromycin and carbomycin. (e) Consideration should be given to maintaining patients treated with Aureomycin and oxytetracycline on a minimum effective therapeutic dose. By so doing there is less likelihood of irritating the intestinal mucosa and of disturbing the normal antagonisms among organisms of the intestinal tract which to some degree may be responsible for inhibiting excessive growth of micrococci; (f) Prompt discontinuance of oral drug therapy is essential if diarrhea occurs on or after the third day of therapy, especially if the diarrhea is of staphylococcal etiology; (g) Since time may be of the essence in certain of these infections (micrococcic enteritis), it appears that sensitivity tests on all phage types prevailing in a given hospital community might be of considerable value in a critical situation. Such tests should include not only the above mentioned drugs, but a variety of combinations of antibiotics to furnish a clue as to the most efficient method of treatment; (h) The antibiotics included as of this time in this problem, penicillin, Aureomycin and oxytetracycline, or such new agents as erythromycin and such old agents as the sulfonamides, are not contraindicated in patients who have diseases which respond to these agents. This is true whether the patients are hospitalized or not and even though resistant strains of staphylococci are known to exist in the hospital population or in a community. The significance of these resistant organisms assumes its proper importance if the possibility of cross-infections is recognized and a rational approach to treatment is made.

18. *The Problem of Burns in Disaster.* CURTIS ARTZ, ERIC REISS, JOHN H. DAVIS, AND WILLIAM AMSPACHER, Fort Sam Houston, Texas. Armed Forces M. J. 4:39–48, January 1953.

Recent international events and the increased emphasis on the use of atomic weapons have created a renewed interest in the management of burns mandatory.

The treatment of burn shock should take precedence over local care. Although a rough guide to fluid replacement can be determined from the weight of the patient and extent of body surface burned, the treatment of shock depends on close clinical observation of the patient and his urinary output during therapy. The local care of burns can be accomplished by the application of dry, fine-mesh gauze dressings or by exposure to the air. A new, one piece, universal protective dressing has been found very useful in the emergency treatment of burns.

Experience with the exposure method in over 250 patients has shown that it is a practicable method of local care. The average healing time of partial-thickness burns was 16 days; 77 per cent of the areas healed without infection. Full-thickness burns were ready for grafting at the time the surrounding partial thickness areas were healed. In the event of a large scale catastrophe, the simplicity of the method may make it the most practicable method of treatment. Its chief disadvantage lies in the fact that it is not applicable to all patients under all circumstances.

therapeutic notes

New Dietary Regime in Ulcer Therapy

Authorities on clinical nutrition have long recognized milk as the prime therapeutic food in the treatment of gastric ulcer. It is not only most effective in neutralizing acid in the stomach, but being rich in protein, vitamins and minerals, it closely follows the dietary needs of the ulcer patient. It is also an important calorie food and contains the required fat needed to inhibit gastric overactivity.

In discussing peptic ulcer in *Dietotherapy: Clinical Application of Modern Nutrition*, Dr. Michael G. Wohl, notes that "the very foods which neutralize acid and give greatest relief from ulcer pain consist of the most nutritious substances in the general dietary." He believes that the ulcer case craves milk and eggs because of the ability of such foods to neutralize acid and that by neutralizing acid, they relieve pain, cause diminution of pylorospasm, and overcome the tendency to vomit. Pointing out that ulcer diets are important and must be followed religiously and without variation, Dr. Wohl puts full emphasis on proteins, particularly milk and eggs. Dr. James S. McLester, in *Nutrition and Diet in Health and Disease*, also stresses that milk comes first in the treatment of ulcer by diet. He states that "it should be the sole food in the beginning, the mainstay of the diet as treatment proceeds and an important adjunct to the menu for many years after a 'cure' has been obtained." Milk is also an essential in the diets outlined by Dr. Clifford J. Barborka in *Treatment by Diet*. The object of the prescribed diet, he points out, is adequate nourishment with the least irritation to the ulcerated surface. He lists the following as important factors in the dietary treatment of peptic ulcer: adequate nourishment with frequent small feedings; avoid mechanically and chemically irritating foods; avoid foods that stimulate gastric secretion; protein foods are desirable; fat foods desirable, and sufficient vitamin content.

Newest development in the field of ulcer dietotherapy is Mull-Soy,* a hypoallergenic food derived from soy beans, which has been used for the past 17 years by physicians in prescribing for patients allergic to milk. The product is now being used for milk-allergic patients who also suffer from gastric ulcer. The number of patients benefited in this way seemed to indicate a definite relationship between the use of Mull-Soy and the diet treatment of ulcers. Work done by individual physicians with nonallergic patients has also met with considerable success.

As a result of the continued favorable individual reports, the Borden Company is initiating studies at several medical schools for a total evaluation of Mull-Soy in the establishment of a new diet regime for the ulcer patient. An examination of the physical content and action of this product points up some of its apparent advantages. This soy bean product exhibits an acid buffer curve similar to or better than that shown by cow's milk. It forms no curd with digestive enzymes and constitutes very finely divided curd particles under the action of gastric acid. Its advantages over milk are that the fat is high in glycerides of the unsaturated fatty acids, particularly linoleic, and that it contains a substantial amount of lecithin.

* Product of the Prescription Products Division of The Borden Company.

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INCORPORATING INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY

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The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

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1. Administrative Psychiatry and Legal Aspects of Psychiatry
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1. Clinical Neurology
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In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

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WINFRED OVERHOLSER, M.D.
Editor-in-Chief

Quarterly Review of **PSYCHIATRY AND NEUROLOGY**

Incorporating the International Record of Psychiatry and Neurology

The Psychologic Implications of Shock Therapy

*D. W. Abse, M.D., D.P.M.**

The workers with considerable experience in shock therapy are often those with little or only superficial psychologic interest, whereas psychiatrists, who largely eschew these methods of treatment, are often those with the greatest degree of such interest. As a result, views of the psychologic implications of shock therapy in mental disorder are often founded upon scanty and desultory observations. This situation has resulted in considerable confusion in the field. There are, of course, intrinsic causes for confusion too, and there are notable exceptions to these general remarks. Thus, Jeliffe,[1] Schilder,[2] Weigert,[3] Good,[4] Bain,[5] Fordham,[6] Plaut,[7] Morrow,[8] Levy and Grinker,[9] Janis,[10] and Silbermann[11] have contributed evidence and theoretical constructions of thought provoking character and immense value.

It is the intention here to resume, and to make additions to, views founded upon observations of patients treated by means of cardiazol, triazol, electricity, and insulin in the various modifications of shock therapy utilized during the passage of the past 13 years. These views have developed with increasing experience, and have been expressed at different phases of development.[12,13,14,15] Observations have taken place in several settings: patients in individual therapy following shock therapy administered by another worker, patients in group therapy following insulin coma therapy administered by others, patients with whom the author has fulfilled the role of both shock therapist and psychotherapist concurrently, and other instances where these roles have been consecutive. It will be appreciated that these are rough statements since any approach to a patient with a healing purpose is immediately psychotherapy whatever else it may consist of too. The cases studied have been diagnosed as various subtypes of schizophrenic reaction, manic-depressive psychoses, involutional melancholic and paranoid reactions, borderline states (that is, mixed psychoneurotic reaction—states where psychotic mechanisms have also been prominent),

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and psychoneuroses, including hysteria and obsessional neurosis. In these latter cases, patients have been in psychotherapy following their exposure to shock therapy previously while in the psychiatric care of others. In a few cases, organic-reaction types have been studied; as, for example, cases of neurosyphilis which in addition to other organic therapy have received electroshock as a means of relieving excitement and depression, so that they could be more adequately managed in specific treatment.

1. *The Traumatic Situation.* Physiologically disrupting events are common to all forms of shock therapy. When such events occur in the organism, these events are immediately and continuously reflected in various ways psychically: this is a never failing observation after exposure to shock therapy. Of course, in general, in therapeutic shock, the physiologic events are rapidly reversible as far as can be usually ascertained; when this does not hold good, we are dealing with a complication from the point of view of therapy. For example, fracture is a complication which is usually slowly reversible, though it might contain some irreversible elements such as some degree of residual deformity, whereas, death is an irreversible complication, fortunately rare in properly conducted treatment.[16] However, it happens that the psychic reflections of disrupting physiologic events are not reversible. *There is always "memory"[*] of such events which can be later inferred from derivatives in the mind of the patient.*

For the most part the reversible physiologically disrupting events take place during altered consciousness or when consciousness is lost. More accurately, part of the disruptive process involves consciousness and is followed by a phase of restitution in which consciousness is gradually regained. The subjective experiences during the disorganization of consciousness, during unconsciousness, and during the restitution of consciousness are all contributive towards the psychic reflections later elucidated in psychotherapy. So also is the complex and changing experience of the patient in his relationship to those responsible for his care during the course of the treatment sessions and between them. The patient is placed into a certain, and to some degree variable, situation in which he is managed sometimes with and sometimes without his full cooperation.

Sometimes the patient's will-to-health and his confidence in the physician may approach that of any one of us who has the task of sitting in the dentist's chair. There is always some degree of anxiety which becomes enhanced or diminished according to experience in this situation. Or the patient, though anxious, may feel he should suffer. The patient is able to recall, and spontaneously and easily does so in later psychotherapy, some of the details, including some of his thoughts and feelings and fancies, during the time he was repeatedly placed in the situation of receiving the treatment. Memory of this kind more or less within the reach of recall, is repeatedly demonstrable in later psychotherapy. However, alone it could not account for the extent to which it becomes apparent in later study that the patient felt threatened, whether he accepted the threat submissively or not. In some modifica-

[*]The persistence of the effects of stimulation upon the living organism is subsumed here under the term "memory." A simple analogy is the camera, a mechanism in which patterns of light are allowed to chemically transform a sensitive film, thus leaving lasting traces upon it.

tions of therapy, which include anesthesia, the patients' conscious recall of operative events is limited to ideas and feelings which preceded the administration of the anesthetic, and those after the shock treatment had been completed.

We have to consider that the traumatic power contained within the memory of the record of events does not account alone for the feelings and elaborations which the patient recounts, nor does it account for later developments which are so deep-reaching. To pursue the former comparison, not much psychic effect could be conceded to an actual experience in the dentist's chair *per se*. Time and again in psychotherapy, the associations of the patient, as they crop up in connection with his experiences of shock therapy, are saturated with anxiety, fears of destruction, ideas concerned with punishment, expiation and making a fresh start. More than this, his aversion to the treatment or his express desire for it are directly related either to his rebellion against a punitive or threatening authority or to his need for punishment because of feelings of guilt. The latter masochistic striving is especially evident in those with suicidal impulses. This constellation of thoughts and feelings, and of fantasies related thereto—intense anxiety, punishment, expiation, rebirth—crop out in connection with shock therapy in the setting of transference phenomena which point up a revival of threatening and punitive parental figures. Nonetheless, these are sometimes credited with "good intentions."

The fact is then that the patient can be shown to have assimilated the experience of a course of shock therapy as a severe threat or as a severe punishment. He does so in such a way as to show that he is affected not merely by the experiences he is able to recall, but that he is moved by unconscious determinants set to action by shock therapy. There is an interaction and intercommunication of feelings and thoughts which occurred during conscious and quasi-conscious periods and those events which occurred when the lights of consciousness were totally extinguished. In short, the patient elaborates psychically from his total experience in the treatment situation, and this includes psychic registration of physiologic events which occurred in the absence of consciousness. Freud[17] showed many years ago that events occurring in the absence of consciousness can exert a powerful intrapsychic effect; this is here corroborated by the later evaluation in analysis of the effects of shock therapy. It happens that memory traces can be laid down in the absence of conscious perceptual organization, and that these traces can exert a very powerful dynamic effect when they link up with previous experiences of tremendous affective importance. As Freud[18] writes about the infant, "the situation of non-gratification in which the amounts of stimulation rise to an unpleasurable height without the infant being able to master them by utilising and discharging them psychologically must be analogous for it to the experience of being born," so it is in essence for the patient exposed to shock therapy.

In shock therapy, the organism is exposed to a traumatic situation repeatedly. In convulsion therapy it happens that the approximation of the physiologic events to the trauma of birth is especially close. Briefly, these treatments involve a repetitive experience which reinstigates a powerful affective signal: we cause the patient to repeat, repeatedly, the pattern of the struggle for life experienced at birth. Jelliffe[1]

formulated the view that the effects of insulin shock were attributable to fear of annihilation, and Schilder[2] came to the view that convulsion therapy operated similarly.

It is this view which enables us to understand the later derivatives of the patient's experience as he comes to express them in psychotherapy. Whenever in psychotherapy the experience of shock is approached by the spontaneous chain of associations of the patient it is always in a typical nexus. To quote common examples: fantasies of being seduced and overwhelmed, fantasies of being beaten or destroyed, fantasies of purgatory—or hell, fantasies of helplessness, fantasies of castration, fantasies of being born again, of forgiveness. These and similar fantasies connect with various levels of anxiety, sometimes operating simultaneously, and give evidence of the powerful anxiety-producing and evoking effects of shock therapy. There are other aspects as well as differences in emphasis in the *modus operandi* of these treatments, and these are adumbrated later.

2. *Mobilization of the Defences.* One may well ask what therapeutic effect could be expected from such psychologic implications of shock therapy? There is no doubt that many patients are, as we see it clinically, and as some of them avow, favorably affected by shock therapy. Two kinds of evidences of benefit may be selected: many show a firmer foothold in reality, many who were depressed become cheerful.

(a). In regard to the first sort of evidence, that of improved reality-testing and of increased interest in the environment, this shows an improvement in ego-functioning. Can this be related to the first condition, that of a repeatedly generated traumatic experience of deep-reaching effect? It is well-known that anxiety is the effector of the defensive operations of the ego. Anxiety, usually reduced only to a signal, is the trigger which sets in motion those mechanisms by means of which the ego struggles to survive. The conscious correlate of this may be put into the simple formula: fear of threatening external danger results in fight or flight. In anxiety set up by unconscious determinants, of course, the relation to reality may be more or less lost, and the struggle of the ego to adjust may be more or less inexpedient from the objective point of view. Adequate and fundamental considerations of this aspect of mental functioning are scattered throughout psychoanalytic literature, the two most important clarifications being Freud's *Inhibitions, Symptoms and Anxiety*[18] and Anna Freud's *The Ego and the Mechanisms of Defence.*[19] In psychologic investigation following shock therapy, one is repeatedly confronted by the intimate relationship of severe anxiety revived by the experiences of physiologic disruption and the defensive efforts made at different ego-levels. The habitual defensive operations are quickly stirred by shock therapy.

It has been shown in previous papers[12, 13, 14, 15] that the improved foothold in reality (when it occurs) is due to an increase in repression accompanied by a shift of interest to the outer world. Anxiety was the original cause of repression, as it was the cause to seek need-satisfying object relationships, and this is precisely the state of affairs reinstituted by means of shock therapy. It is also necessary to point out that other defences are mobilized in shock therapy; in some instances, for example, regressive and projective defences may be predominantly aroused with un-

favorable results. This is one among many considerations which should influence the selection of the patients to be exposed to these drastic methods of treatment.

In general, the exhibition of repetitive traumatic situations resulting in anxiety, repression, and extraversion is but one important aspect of the induction of a repetition of the history of the ontogenetic evolution of the synthetic, defensive, and executive functions of the ego. When these functions have become grossly disturbed, shock therapy is a drastic and desperate attempt to stimulate them anew.

(b). The second point of outstanding clinical importance is the relief of depression sometimes afforded by shock therapy. A partial aspect of the matter is that depression represents a state of tension between the super-ego and the ego. In psychotherapy, following shock treatments, it is very clear that the need for punishment experienced by the guilt-laden depressive has been to a greater or lesser extent satisfied by the traumatic events. It is the relief afforded by a whipping to the guilty child, and associations and reminiscences of this order crop out in connection with verbalization of experiences during the course of shock treatment. In itself, this already implies the therapeutic limits and deficiencies of shock therapy. One has further to appreciate that as unwelcome id impulses crystallize as wishes and reach towards conscious representation that the ego is often capable of adequate defence by means of repression, sometimes supplemented by other defensive manoeuvres too—as the movement from impulse to wish occurs anxiety is generated and leads to defence. It is when the defences are inadequate for one or another reason, that the super-ego tension is generated and results in conscious feelings of depression and morbid ideation. Sometimes, the ego utilizes a characteristic "last-ditch" defence when there is partial failure of repression and other defences. This we note clinically as psychomotor retardation. Thinking and motility are partially paralysed so that the avenues to conscious formulation and motoric expression are blocked. Such massive outer defences are a characteristic manifestation in psychosis. When by means of shock treatment, anxiety is regenerated, repression becomes more effective. The ego, defending itself more effectively, no longer arouses the wrath of the super-ego, and no longer needs the bulwark of retardation.

The clinical result of cheerfulness and disinhibition has been wrongly interpreted, in my opinion, by some workers in the field as evidence of shock therapy effecting an undoing of repression.[9] This has led to a confusion of the psychologic implications of shock therapy. The relief of the need for punishment and the repression producing effects of shock therapy are part and parcel of the same process. Repression is itself partly a masochistic type of defence: the ego sequestrates part of itself or part of that which is beginning to organize within itself. There are, of course, biologic analogies in the most primitive organizations of protoplasm.

3. *Loving Care.* In the experience of many psychiatrists insulin therapy is found to be more effective than other shock methods in inducing a remission of schizophrenic disorganization. In the author's opinion, this is due to the more emphatic stress in insulin therapy on the "loving care" aspect of shock treatment. So far, in this paper, discussion has centered about the anxiety producing and punishment involvements of shock therapy in the (unconscious) minds of the patients exposed to

this treatment. One could devote more consideration of this darker side, as well as the "loving care" aspect, as they are involved in the minds of the physicians and nurses. After all, the patient, his physician, and the nurses are all involved in a nexus of interpersonal relationships with conscious and unconscious percussions and repercussions.

As far as the patient is concerned, he knows or gets to know that efforts, however misguided he may conceive them to be, are being made ostensibly to cure him of what he may, or may not, acknowledge to be his disease. Even this partial statement may be useful insofar as it indicates something of the polyphony of thought which is later uncovered in analytic anamnesis. In insulin therapy there is considerably more sustained and assiduous individual attention; this is required by the actual mechanics of the treatment. Moreover, the type of physiologic disruption is of a specifically hunger-producing kind. Many patients express their intensive oral needs and longings which they felt on awakening from coma, and the gratitude they felt to the nurse who gave them the sugared juices after termination of coma. We also have to consider the consequences of hypoglycemia during unconsciousness—these too are written in, as it were, and exert powerful dynamic effect. This treatment, to a higher degree than the other shock therapies, comprises a process of "blowing hot and cold," of putting the patient into a traumatic situation and then of rescuing him from it. More than this, it comes to emphasize hunger and feeding. This becomes tied up in the patient's mind with experiences at the breast, often with a mother whose love was decidedly provisional: he must allow himself to be managed and then all would be well. Thus insulin therapy flavors the traumatic situation with additional elements, as well as a more pronounced emphasis upon loving care. More intensive efforts at observation of the total process in insulin therapy of schizophrenia are needed. Even these few comments suggest, however, that the differential response of affective and schizophrenic disorder, the one more markedly to convulsion therapy and the other to insulin coma therapy, is connected with the respective ratios of loving care to "threat and punishment," both aspects reaching the patient at deep unconscious levels of his mental functioning.

4. *Psychotherapeutic Disadvantages of Shock Treatment.* There are patients who are quite inaccessible, and whom shock therapy enables to relate sufficiently to make psychotherapy a possibility. This should be fairly recognized and it is unwise to make wildly expansionist claims for psychotherapy. There are patients who with some few therapists[20] are able to gain ground even from acute schizophrenic disorganization. Even in some of these cases, however, the first stages of treatment, and sometimes further stages of treatment, are for the most part in the direction of rerepression.[21,22] This is often far more quickly accomplished by means of shock therapy and often cannot be accomplished at all without the intervention of organic therapy.

This opinion does not, however, lead to the view that patients should be indiscriminately exposed to shock therapy. These treatments, on the contrary, should be used only *faute de mieux*,[15] because there are serious psychotherapeutic disadvantages associated with their exhibition.[8] The appeasement of the masochistic strivings of

the patient results in additional difficulties in helping the patient to develop out of a sado-masochistic organization in later psychotherapeutic work. The patient needs help to enjoy life and not merely to submit to it. In general, shock therapy operates along with the defences of the patient so that he may later be even more frightened of relinquishing inexpedient and self-sacrificing devices than he was before the onset of his illness. When there are considerable ego-assets which make psychotherapeutic work with the patient especially rewarding, shock therapy is to be avoided if at all possible. In all cases, adequate study of the patient, and attempts at psychotherapy, should be made before the resort to shock treatment. Following its unavoidable utilization, it is my experience that individual or group psychotherapy can do much to mitigate its disadvantageous effects.

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ABSTRACTS

psychiatry

ALCOHOLISM AND DRUG ADDICTION

61. *The Psychological Mechanism of Alcohol Addiction.* ALBERT D. ULLMAN, Medford, Mass. Quart. J. Studies on Alcohol. *13*:602–08, December 1952.

Efforts to find a unitary cause of alcohol addiction not only have been unsuccessful, but have obscured the issue which the author believes to be central: the mechanism whereby an addiction comes into being. Based on the analogy of experimental work with rats in which a kind of eating behavior which has "addictive" or "compulsive" components, suggestions are made concerning the conditions under which alcohol addiction is likely to occur. It is posited that (*a*) when a person is highly motivated to drink or there is some emocional arousal with regard to drinking, and (*b*) such drinking is accompanied by a stress situation, and (*c*) these circumstances occur on several occasions when a sufficient amount of alcohol is imbibed to produce a tension-reducing effect, then alcohol addiction will result.

It is suggested, accordingly, that therapy ought to be directed toward altering the habit systems of the alcoholic by substituting other tension-reducing activities for drinking. This may obviate the quest for specific underlying causes of alcoholism which probably do not exist. 16 references. —*Author's abstract.*

62. *Some Applications of a Follow-Up Study to Psychiatric Standards for Mobilization.* NORMAN S. BRILL AND GILBERT W. BEEBE, Washington, D. C. Am. J. Psychiat. *109*:401–10, December 1952.

The experience of World War II suggests that another large-scale mobilization will necessitate the use of marginal personnel including those with emotional disorders to a greater extent than was the case in World War II. There is need for a more careful assessment of military manpower requirements in terms of capacity to function at a wide array of jobs, and not just in combat. The type of psychiatric examination possible at induction has proved to be inadequate for forecasting military performance and, therefore, in itself cannot be relied upon for the proper selection of individuals for service. Its value is confined to the elimination of only the more obviously inapt and the grossly ill.

One million men who served without requiring psychiatric care would have been lost to the army in World War II had all psychiatrically predisposed men been rejected, and even those who required psychiatric care appear to have paid their way as a group. Criteria for evaluating military performance seem badly needed.

Predisposition has been emphasized in the past, to the neglect of the importance of stress in causing breakdown. In only 5 per cent of the 955 follow-up cases did breakdown occur without apparent stress, and in more than 80 per cent (regardless of the amount of predisposition) the major stress was military in nature. Resistance to military stress generally, and to ground combat in particular, varies greatly with age; older men having much higher rates of admission for psychiatric care. Except for those who seemed entirely normal at entry, combat seems to produce somewhat more disability than other forms of military stress.

About 35 per cent of all army World War II admissions for psychoneurosis were men who had no psychiatric difficulty before entering the service. As seen upon follow-up five years after breakdown, there is little change in those who were previously normal or overtly neurotic, and a moderate worsening of the emotional health of those with personality disorders, neurotic traits, and suggestive neuroses. 8 references. 4 figures. 6 tables.—*Author's abstract.*

CLINICAL PSYCHIATRY

63. *The Management and Treatment of the Manic-Depressive Syndrome in An Occupational Therapy Clinic.* BETTYANNE STEICHEN CONDON, Minneapolis, Minn. Am. J. Phys. Med. *31*:415-21, December 1952.

Carefully written prescriptions to an occupational therapist in a psychiatric clinic are necessary if the therapist is to treat the patient intelligently and enable him to receive full value of the therapies she has to offer. The therapist should know: patient's name, age, sex, diagnosis, presenting symptoms, brief history of the illness, attitude prescribed, and treatment aim.

To illustrate how an occupational therapist can participate in the treatment program of the mentally ill patient two cases are described. Here is a brief abstract of the discussion following presentation of the patient's activities in the occupational therapy clinic. The treatment aim of a patient presenting symptoms of the manic-depressive syndrome in the manic phase was to learn to relax and calm down.

It is not so important what the patient makes in occupational therapy, as what aspects of activity are stressed. Manic patients are usually calmed by quiet repetitive activities. When the patient did weaving, he was given a soft wool and a simple pattern so that the beating would be subordinated to the repetitive, quieting activity. The patient gradually learned to control his behavior and lost his fear that others would become excited when he was excited. He tested the therapist by falling and learned that his behavior did not upset her. He learned to accept reality by being constantly faced with it. The therapist tried to make reality attractive to him by showing him constructive ways of getting attention and complimenting him when he had done the right things. In planning projects the therapist also had to take care that the patient, in his impulsiveness and overactivity, did not ruin the project, thereby adding to his feelings of loss of self-esteem. He needed praise for acceptable behavior and accomplishment, but the

occupational therapist had to help him so that he could realistically earn this praise. This was accomplished by carefully guiding him in simple, short-term projects that would be nice to look at. Care was taken so that he would not feel rejected, since a feeling of rejection works right in with the depression underlying the manic state.

The treatment aim of the patient presenting depressive symptoms of his illness was to relieve the depression. Initially, all depressed patients are given a task to do by the occupational therapist. One patient was given sanding to do because this is a menial, monotonous task that he could interpret as punishment, thereby helping him to atone for his guilt feelings. The therapist, by repeatedly reassuring the patient that he was not going to ruin the project, impressed upon him that she could control his destructive impulses in the shop. At no time during the patient's depressed phase is he given a direct compliment. Praise only further adds to his guilt feelings. Occasionally, however, the therapist remarks about the work the patient is doing, such as, "This bookcase looks better," or "The rug is going to be very useful." Compliment expressed in this fashion will be interpreted by the patient according to his need at the time. The therapist carried out the attitude prescribed of kind firmness by being very definite about what the patient should do, and reassuring him when necessary, especially after shock treatment. But she used her reassurance, not in a solicitous way, but rather to interpret reality. Patients in shock therapy can be greatly assisted in their return to reality by assigning them projects requiring familiar movements and patterns. The project or job given to a depressed patient, no matter how menial or monotonous, should always be a useful one, since one of the goals in his treatment is to reestablish a feeling of worth.

GERIATRICS

64. *The Aged Mental Hospital Patient.* WILLIAM FORSTER, Brandon, Manitoba, Canad. M. A. J. 68:29-33, January 1953.

The entire population aged 70 or over of a British mental hospital was examined (178 females, 81 males). The great majority of those breaking down at 60 years of age or less did so in middle age or the involutional years: in the females schizophrenia preponderated (55 per cent), in the males affective reactions (53 per cent) as the cause of long-stay hospitalization. An appreciable number of this group developed features indistinguishable from organic dementia; this was not related to the length of hospitalization or to any particular psychosis, and it developed more frequently in females. It is suggested that the hospital environment by encouraging apathy may contribute to apparent intellectual atrophy. In the breakdowns of the involutional period and later, with survival to a good old age, the only type of schizophrenia of importance is the paraphrenic. In the patients breaking down for the first time in old age (61 plus), only about 60 per cent in each sex showed senile or arteriosclerotic psychosis. The generally unrealized but high incidence of functional reactions in the senium reported by other authors is underlined. Of either sex with senile psychosis (37 females, 16 males), a fourth showed

predominantly an affective picture, a fourth a paranoid, and half simple deterioration. In those with a paranoid coloring the delusions were absurd and adapted to the hospital environment. They were misinterpretations rather than projections. Only one patient of each sex had a frankly schizophrenic picture and these had an hereditary loading. It is suggested that probably the only true senile psychoses are simple deterioration and deterioration with secondary delusions. In other varieties the affective or schizophrenic components should be seen as such and as independent of the primary psychosis or the result of disinhibition. These components are likely to be those that bring the patient to hospital. 13 references, 3 tables.—*Author's abstract.*

PSYCHIATRY AND GENERAL MEDICINE

65. *The Psychosomatic Concept in General Medicine.* EDWARD WEISS, Philadelphia, Pa. J. M. A. Georgia. 47:536–40, December 1952.

One third of all patients with chronic illness are "functional" cases in most of whom emotional factors are responsible for the bodily illness. In another one third of such patients, emotional conflict adds to the burden of physical disease. Thus, the majority of patients present psychosomatic problems. Psychosomatic medicine is not a new speciality; it is an approach to medical problems that involves two methods of study—physiologic and psychologic. It does not mean to study the body less; it only means to study the psyche more. A new approach to an old subject, it substitutes a scientific process (psychodynamics) for intuition (the "art" of medicine). It leads to a definitive diagnosis and prepares the way for comprehensive medical care which includes minor psychotherapy. Major psychotherapy is the job of the psychiatrist, but the general physician must know the indications and how to make a referral. 9 references.—*Author's abstract.*

66. *The Liaison Psychiatrist: His Role in Gynecology.* MARK LEWIS GURSTLE, JR., New York. Bull. N. Y. Acad. Med. 29:249–57, March 1953.

In general the paper concerns itself with the rôle of the liaison psychiatrist at The Mount Sinai Hospital, New York City, and points up the significant impact such psychiatrists have made on all the inpatient and outpatient services of the hospital. In particular the paper deals with the specific character of the liaison psychiatrist on gynecology. Gynecology, involving as it does the reproductive structures of a woman, obviously brings into special prominence feelings common to all patients faced with surgery, including ideas relative to deprivation, castration, and destruction of the body image.

In general the duties of the liaison psychiatrist fall into four categories: (1) to concern himself with the welfare of patients; (2) by his general attitude to formulate an example to the other clinicians in what he considers to be a proper approach to patients; (3) to strive for indoctrination of the staff in the psychosomatic point of view or what better can be called the technic of comprehensive medicine.

and (4) to interest himself in original investigative work which may prove a contribution to research.

Lastly, the rôle of a liaison psychiatrist on gynecology is a highly challenging and provocative one in which the various disciplines and foci of interests of all concerned can be combined in a way which eventuates in better and more complete care for the patient. 4 references. — *Author's abstract.*

67. *Motility of the Small Intestine During Emotional Reactions.* HAROLD P. ROTH, RAYMOND N. FERRERI, MICHAEL A. PETTI, AND MARVIN W. EVANS, Cleveland, Ohio. Ann. Int. Med. *38*:38–52, January 1953.

The motility of the small intestine was recorded by the balloon-tambour method in 20 patients during psychiatric interviews in which an attempt was made to elicit and evaluate emotional reactions. Significant emotional reactions were observed on 34 occasions but during only 7 of these was there simultaneously a definite change in intestinal motility. At many other times during the interviews it was difficult to evaluate the patient's emotional status or the significance of changes in intestinal motility. Thus, it was often hard to determine what specific emotion a patient was experiencing as some were having several emotions at the same time, whereas others were merely anxious. The intensity of the emotion could only be roughly estimated by the interviewer. A definite control period was difficult to obtain as many patients were apprehensive in the preinterview period, restless in the postinterview period, and during the interview itself either never relaxed, or appeared relaxed and were found not to be. The intestinal motility records were hard to evaluate as there was such spontaneous variation in the motility that it was difficult to decide that any change was due to the patient's emotional status at that time. The wave pattern was also so irregular that it was impossible at times to determine tone or distinguish peristaltic waves.

There were, however, some suggestive findings. In one patient there appeared to be a rise in intestinal tone 4 out of 5 times when he discussed a physician whom he disliked. In another patient there was persistently elevated tone during one interview conducted just after he received a parking ticket and during which he continually reverted to topics about policemen and parking, even though an effort was made to distract him. A third patient did not show emotion as he discussed socialized medicine during the interview but did have elevated tone. He brought the subject up again one half hour after the interview was over and again developed increased tone. A fourth patient became angry at the examiner's questioning. He was definitely more angry than the others, was breathing deeply and clenching and unclenching his fists. His tone appeared to be elevated, but when he stopped breathing deeply it was actually low. A number of patients developed symptoms during their interviews, such as vomiting and abdominal pain, generally symptoms that they had complained of on admission to the hospital. Only twice was there a correlated change in intestinal motility. 14 references. 4 figures. 1 table. — *Author's abstract.*

PSYCHIATRIC NURSING, SOCIAL WORK AND MENTAL HYGIENE

68. *Psychiatry and the Neuropsychiatric Technician.* BERNARD I. KAHN, Oakland, Calif. Med. Technicians Bull. 7:10–11, January, February, 1953.

In the parade of history the neuropsychiatric technician has progressed a long way from a guard with a whip and manacles to his present professional status: an expert, trained in the practical application of interpersonal relations. The patients treated by these technicians are frightened, anxious about their future, depressed and lonely. Tense and uneasy, they are unable to work effectively with their shipmates.

The three avenues by which people handle their emotional problems are: by aggressive impulses which may or may not be realistic; by running (withdrawal), which may be immature; or by asking for help (dependency).

The ramifications of these dynamic avenues are, of course, endless. Today the Navy handles the emotional problems of men by placing them as promptly as possible under the care of a psychiatrist, where he is under the constant surveillance of the neuropsychiatric technician. The training of this technician is of paramount importance, and the Neuropsychiatric Technicians School at the U. S. Naval Hospital, Oakland, California, emphasizes the patient's treatment is accomplished in large part through the technician's observation; and he is taught that he is, in essence, the eyes, ears, hands, and voice of the doctor.

The training attempts to inculcate it is only in maturity that one can really find inner peace, satisfaction, and freedom from plaguing worries, obnoxious thoughts and the dreary fears remaining from childhood.

The following assets are needed to become a good neuropsychiatric technician: (1) An innate respect for the dignity and feelings of one's fellow man and a deep interest in self-respect; (2) sufficient maturity to accept insults from sick men — who may, in consequence of their illness, act like children — without showing scorn, resentment or ridicule; (3) understanding and tolerance for the bewildered and unhappy; and the ability to look at a disturbed patient with humility and sympathy, and be able to feel compassionately: "There, but for the grace of God, am I."

69. *Ethical and Psychological Aspects of a Group of Adolescent Misfits.* G. AMADO, France. L'Evolution Psychiatrique. *13* 30, 1952.

The author studied the "Dupont-Latin Group," which consists of 100 to 200 adolescents who had selected as a meeting place the Dupont-Latin coffee house in the Latin Quarter in Paris. Setting forth first the origins of the group, the author emphasizes the significance of the spatial factor. Life in the Latin Quarter, as a matter of fact, is governed by a very definite ritual which contributes to unite the group. It is essentially a life of idleness. In order to eat, the members of the group depend on semibeggary. Idleness, combined with pressing needs for food, naturally leads to all forms of deliquency. The structure and the limits of the group

are rather poorly defined. The main characteristic features of the group include the following: most of its members have a bourgeois origin; they have aspirations to originality, as well as to intellectual and artistic superiority; in most cases, they adhere to an existentialism, poorly understood. The only productions of the group consist of a few poems or drawings.

Before reporting on approximately 10 clinical cases distributed in three categories according to the gravity of the prognosis, the author reviews the individual factors of the organization of the group: he observes difficulties inherent in the puberty stage which lead the adolescent to enter into rebellion, more or less openly, against his family and against society, then, to quiet his guilt feelings, to join a group where he can exchange the standard moral values for a group ideal which enhances and approves his behavior and offers him the guarantee of a presumed existentialism or factitious intellectuality. The author concludes his study by indicating possible methods of rehabilitation.

neurology

CLINICAL NEUROLOGY

70. *Tension Headache.* ARNOLD P. FRIEDMAN AND THEODORE J. C. VON STORCH, New York. J. A. M. A. *151*:474–77, Jan. 17, 1953.

Tension headaches may be separated from migraine, conversion (hysterical), muscular, and other types of headache. For this study the authors selected 100 consecutive cases of tension headaches seen at the Montefiore Hospital Headache Clinic for a period of one to four years. The material was analyzed according to age, sex, presence of prodroma, location, frequency, intensity, and duration of headaches, associated symptoms, family history, precipitating factors, and response to symptomatic and prophylactic treatment. Physical, neurologic and psychologic examinations were performed on each patient. Many had special laboratory examinations including roentgenograms of the skull and cervical spine, visual field determination and complete blood examination. Tension headache should be limited to cranial pain occurring in relation to constant or periodic emotional conflicts which may be conscious or unconscious. Such an emotional state may induce headache by producing changes in the caliber of the cranial vessels and spasm of the skeletal muscles of the head and neck. Tension headaches have no prodroma, are usually bilateral, occipital, or frontal and may be accompanied by a variety of associated signs, including anxiety, nausea, and vomiting. Frequency and duration is variable.

As with most headaches, a variety of psychogenic factors may be associated with tension headaches. In a majority of the authors' cases, the fundamental psychologic factors were largely unconscious, although 72 per cent were aware of their anxiety. Environmental demands of an economic and social nature beyond the

capacity of the patient's personality may also produce somatic response of which headache is the major reaction. The best symptomatic therapy is obtained by analgesics and sedatives (64 per cent). The best prophylactic results are obtained by psychotherapy (58 per cent). Patient-physician relationship is of prime importance in the treatment of these headaches. 6 references. 2 figures.—*Author's abstract.*

71. *Neurological Complications Following Antirabies Vaccination.* EMANUEL APPELBAUM, MORRIS GREENBERG, AND JACK NELSON, New York. J. A. M. A. *151*:188–91, Jan. 17, 1953.

Experience in 46 cases of encephalomyelitis following vaccination with rabies virus in New York City from 1928 to 1951 is summarized. The cause of this form of encephalomyelitis is not clear but is believed to be a sensitization phenomenon. The cause of this form of encephalomyelitis is not clear but is believed to be a sensitization phenomenon. The onset was usually sudden with chills, fever, headache, vomiting, and changes in the mental state. The clinical picture varied, depending on the type of neurologic involvement. In 37 patients the clinical manifestations were those of meningoencephalitis, with meningeal signs, cranial nerve involvement, paralysis, tremors, ataxia, and dysarthria. Five patients showed a dorsolumbar myelitis, with paraplegia, anesthesia, and loss of sphincter control. In the remaining 4 cases the picture was mainly one of peripheral neuritis. The spinal fluid was usually clear, with an increase in cells, predominantly lymphocytes. The clinical course was, as a rule, short, with recovery occurring in one or two weeks. In some cases progress was slow and recovery gradual. No specific therapy was employed. There were no deaths in the series. Sixty-four per cent of the patients made a complete recovery and thirty-six per cent had some neurologic residua.

The incidence of encephalomyelitis was one accident to 2,025 persons treated in New York City Department of Health clinics, but it was about five times higher in those who received 14 injections than in those who received 7 or fewer injections. The risk of rabies from a bite is shown to be greater than that of encephalomyelitis from vaccination. Since the use of antirabies vaccine exposes the persons treated to the risk of encephalomyelitis, there is good reason for establishing fairly rigid criteria for its administration. The New York City Department of Health at present advises antirabies vaccination only after a bite by a rabid animal, by a suspiciously rabid animal until its status has been determined, or by a stray dog that cannot be apprehended. The use of an antirabies vaccine that does not contain brain tissue would probably eliminate the danger of encephalomyelitis. Antirabies serum has been used very little and cannot be properly evaluated as a prophylactic measure against rabies. 19 references. 4 tables. *Author's abstract.*

CONVULSIVE DISORDERS

72. *Mesantoin in the Control of Epilepsy.* ANTHONY L. LOSCALZO, New York. Neurology 2:403–11, Sept.–Oct. 1952.

Of 224 patients with epilepsy treated with mesantoin, 154 had grand mal sei-

zures, 50 psychomotor epilepsy, 24 petit mal seizures (predominantly with occasional grand mal seizures in 14 patients), 10 had focal convulsions, and 6 Jacksonian epilepsy. Most of these patients had been receiving dilantin, and mesantoin was substituted in corresponding dosage, until dosage could be modified after eight to twelve weeks' trial. The dosage of mesantoin employed in these cases varied from 1 to 10 tablets daily, the average daily dose being 5 tablets (0.5 Gm.); phenobarbital was given with mesantoin in a daily dosage of about 1⅔ grains. The number of expected grand mal seizures for a year was calculated as 8,379 and the number of seizures occurring during the first year of mesantoin therapy was 4,228, a reduction of nearly 50 per cent. Grand mal seizures were entirely abolished in 66 cases; reduced from 10 to 90 per cent in 116 cases; not reduced in 22 cases; and increased in 20 cases. No attempt was made to keep actual counts of petit mal, psychomotor, or Jacksonian episodes. The drug had little or no effect in petit mal, seizures were increased in some cases; there was some decrease in psychomotor attacks, but this was not regarded as statistically significant. The chief side effects of mesantoin therapy were drowsiness, occurring in 36 cases (16 per cent); rash in 22 cases (9 per cent) and gingival hypertrophy in 7 cases (3 per cent). Complete blood counts showed that 12 patients (5.5 per cent) had a mild pancytopenia without rash or other symptoms, not requiring discontinuance of the drug, and 1 patient had a moderate pancytopenia that necessitated careful observation. Mesantoin is less toxic than other hydantoins, and a better anti-epileptic drug than dilantin, in the author's experience. For best results dosage must be adjusted carefully in each case. Treatment should be begun with caution in patients with a history of allergy or drug sensitization; and patients requiring a dosage of over 0.8 Gm. daily should be under careful observation. If rash, abnormal vaginal bleeding or bleeding from the gums occurs, the drug must be discontinued. Less severe symptoms, such as pruritus, lacrymation, canker sores, or postauricular exfoliation, indicate a reduction in dosage and careful observation of the patient. 47 references. 1 figure (graph). 1 table. *Author's abstract.*

book reviews

The Maggid of Caro. HIRSCH LOEB GORDON, New York, N. Y. Shoulson Press, 1949. 396 pages.

The author, a psychiatrist of wide learning in other fields (notably history and linguistics), presents here a discussion, based on his own translation of the diary of a learned and highly influential Jewish rabbi, Joseph Caro. Caro was born in Toledo, Spain, in 1488, but his parents along with the rest of the Jews, were expelled from Spain by Ferdinand and Isabella in 1492, making their way via Turkey and Palestine. There Caro lived, honored and revered, until his death at the age of 87. The significant feature of his life for our present purpose is that 71 years

after his death there was published his secret diary containing in great detail the messages received from his private daemon (as Socrates would have termed him), or Maggid, over a period of 52 years or more.

The book gives a wealth of extracts from this diary (first translated into English by Dr. Gordon), and raises a host of questions as to the place in religion of what we today term hallucinations—a topic discussed eloquently fifty years ago by William James, and one which comes up frequently in the study of such historic religions not only as Judaism, but also Buddhism, Mohammedanism, and Christianity. This volume is a valuable addition to the literature of the psychology of religion; it illustrates once again the fact that what in ordinary parlance we may term hallucinations are in certain circumstances not only not inconsistent with, but may actually reënforce religious experience and wide social usefulness.—*Winfred Overholser, M. D.*

Books Received for Review

Physiology of the Circulation of the Brain: an annotated bibliography, Washington, D. C. American Physiological Society, 1938–1948. Supplement No. 1. July 1952. 437 pages. Price $4.50.

Archivos de Neurocirurgia año 1949. Report of proceedings—third South American Congress of Neurosurgery. Buenos Aires.

Specific Dyslexia. BERTIL HALLGREN, Copenhagen. Ejnar Munksgaard, 1950.

Pronostic des Troubles du Caractère chez l'Enfant. Symposium from the First International Congress of Psychiatry, Paris, France. Sauvegarde de l'Enfance, 1951.

The Hypersensitive Mind. GABRIEL LANGFELDT, Copenhagen. Ejnar Munksgaard, 1951. 146 pages.

A Study in Manic-Depressive Psychosis. AKE STENSTEDT, Copenhagen. Ejnar Munksgaard, 1952. 111 pages. Price 20 kroner.

Psycho-Infantilism. BENGT J. LINDBERG, Copenhagen. Ejnar Munksgaard, 1950. 126 pages. Price 7 kroner.

Psiquiatria (Tomo I). EMILIO MIRA Y LOPEZ, Buenos Aires. El Ateneo, 1952. Fourth Edition.

Problems of Consciousness: Transactions of the Third Conference. Edited by HAROLD A. ABRAMSON, New York, N. Y. Josiah Macy, Jr., Foundation, 1952. 156 pages. Price $3.25.

Office Psychiatry. L. G. MOENCH, Chicago, Ill. Year Book Publishers, 1952. 310 pages. Price $6.00.

Understanding That Boy of Yours. MELBOURNE S. APPLEGATE, New York, N. Y. Public Affairs Press, 1953. 52 pages. Price $1.00.

NOTES AND ANNOUNCEMENTS

The QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is glad to welcome to the field of psychiatric publications LA REVISTA DE PSIQUIATRIA Y PSICOLOGIA MÉDICA DE EUROPA Y AMERICA LATINAS.

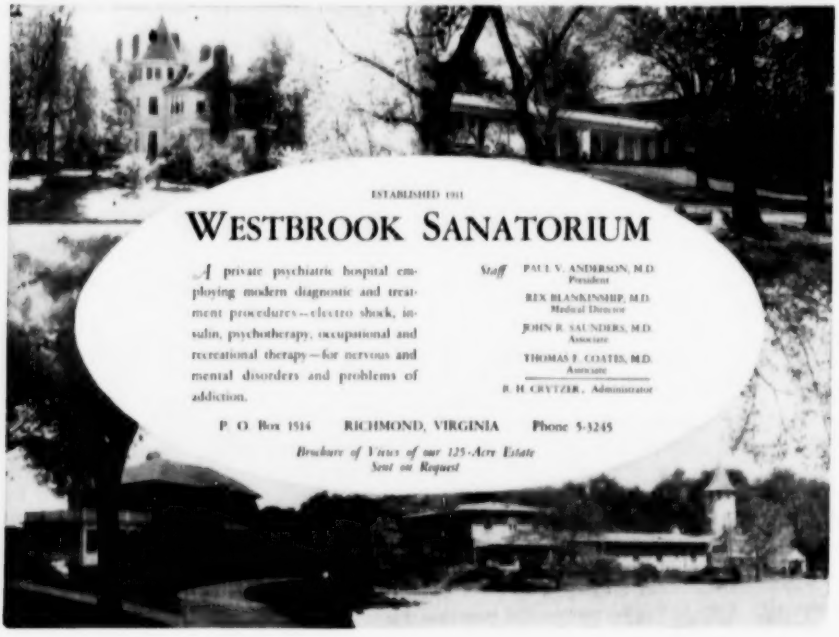
The first issue contains a preliminary statement by Prof. R. Sarró B. of Barcelona, the editor, and articles by Profs. Delgado of Lima, Vallejo Nágera of Madrid, and Llorente of Valencia, as well as book reviews, abstracts, and news items.

Prof. Sarró is assisted in the editorship by Professors Obiols and Vallejo Nágera and a distinguished staff of collaborating editors. The journal, which will appear bimonthly, is published by Editorial Scientia, Barcelona.

At the Thirty-Second Annual Meeting of the Association for Research in Nervous and Mental Disease held in New York City, 1952, the following officers were elected for the year 1953:

President	Dr. Davenport Hooker
1st Vice-President	Dr. John C. Whitehorn
2nd Vice-President	Dr. Lawrence H. Snyder
Secretary-Treasurer	Dr. Clarence C. Hare
Assistant Secretary	Dr. Rollo J. Masselink

The subject for the 1953 meeting will be "Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns."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